

CLAIMS

What is claimed is:

1. A method for developing ligands binding to PDE5A, comprising
identifying as molecular scaffolds one or more compounds that bind to a binding site of PDE5A;
determining the orientation of at least one molecular scaffold in co-crystals with PDE5A; and
identifying chemical structures of said molecular scaffolds, that, when modified, alter the binding affinity or binding specificity or both between the molecular scaffold and PDE5A; and
synthesizing a ligand wherein one or more of the chemical structures of the molecular scaffold is modified to provide a ligand that binds to PDE5A with altered binding affinity or binding specificity or both.
2. The method of claim 1, wherein said molecular scaffold is a weak binding compound.
3. The method of claim 1, wherein said molecular scaffold binds to a plurality of phosphodiesterases.
4. A method for developing ligands specific for PDE5A, comprising
identifying a compound that binds to a plurality of phosphodiesterases; and
determining whether a derivative of said compound has greater specificity for PDE5A than said compound.
5. The method of claim 4, wherein said compound binds to PDE5A with an affinity at least 10-fold greater than for binding to any of said plurality of phosphodiesterases.
6. The method of claim 5, wherein said compound interacts with at least one conserved PDE5A active site residue.

7. The method of claim 4, wherein said compound binds weakly to said plurality of phosphodiesterases.

8. The method of claim 4, wherein said plurality of phosphodiesterases comprises PDE5A and PDE6.

9. The method of claim 4, wherein said plurality of phosphodiesterases comprises PDE5A and PDE11.

10. A method for identifying potential PDE5A binding compounds, comprising identifying a molecular scaffold that binds to PDE5A; and fitting at least one electronic representation of a compound in an electronic representation of a PDE5A binding site, wherein said compound is a derivative of said molecular scaffold.

11. The method of claim 10, wherein said electronic representation of a PDE5A binding site is defined by atomic structural coordinates set forth in Table 1.

12. The method of claim 10, comprising removing a computer representation of a compound complexed with PDE5A and fitting a computer representation of a compound from a computer database with a computer representation of the active site of PDE5A; and identifying compounds derived from said molecular scaffold that best fit said active site based on favorable geometric fit and energetically favorable complementary interactions as potential binding compounds.

13. The method of claim 10, comprising modifying a computer representation of a compound complexed with PDE5A by the deletion or addition or both of one or more chemical groups; fitting a computer representation of a compound derived from said molecular scaffold from a computer database with a computer representation of the active site of PDE5A; and

identifying compounds derived from aid molecular scaffold that best fit said active site based on favorable geometric fit and energetically favorable complementary interactions as potential binding compounds.

14. The method of claim 10, comprising
removing a computer representation of a molecular scaffold or a derivative compound thereof complexed with PDE5A and; and
searching a database for compounds having structural similarity to said molecular scaffold or derivative compound using a compound searching computer program or replacing portions of said compound with similar chemical structures using a compound construction computer program.

15. The method of claim 10, wherein said compound complexed with PDE5A is non-hydrolyzable cGMP analog.

16. The method of claim 10, wherein said fitting comprises determining whether a said compounds will interact with one or more of conserved PDE5A active site residues.

17. A method for attaching a PDE5A binding compound to an attachment component, comprising
identifying energetically allowed sites for attachment of a said attachment component on a phosphodiesterase binding compound; and
attaching said compound or derivative thereof to said attachment component at said energetically allowed site.

18. The method of claim 17, wherein said attachment component is a linker for attachment to a solid phase medium, and said method further comprises attaching said compound or derivative to a solid phase medium through a linker attached at a said energetically allowed site.

19. The method of claim 17, wherein said phosphodiesterase comprises conserved residues matching at least one conserved PDE5A active site residues.

20. The method of claim 18, wherein said linker is a traceless linker.

21. The method of claim 18, wherein said phosphodiesterase binding compound or derivative thereof is synthesized on a said linker attached to said solid phase medium.

22. The method of claim 21, wherein a plurality of said compounds or derivatives are synthesized in combinatorial synthesis.

23. The method of claim 18, wherein attachment of said compound to said solid phase medium provides an affinity medium.

24. The method of claim 17, wherein said attachment component comprises a label.

25. The method of claim 24, wherein said label comprises a fluorophore.